Ponatinib Induced Pityriasis Rubra Pilaris: Case Report and Review of Literature

Dear Editor,

Pityriasis rubra pilaris (PRP) is a papulo-squamous eruption characterized by follicular keratotic papules coalescing to form orangish plaques and islands of sparing.

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI), approved in 2012 by the United States Food and Drug Administration for chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia.[1] The most common adverse effect of ponatinib is skin rash and xerosis, seen in around half of the cases.[2] Here, we present a case of PRP-like eruption in a patient receiving ponatinib for CML.

A 45-year-old woman was referred from hematology services for evaluation of mildly itchy, scaly red rashes on her buttocks, lateral aspect of thighs, elbows, and abdomen of 10 days duration. The patient was a known case of CML and had failed treatment with imatinib and nilotinib. Based on the mutational analysis for T315I, ponatinib 45 mg daily was recently instituted. Around two weeks after the initiation of the therapy, the patient developed a skin rash. Examination revealed folliculocentric papules on the abdomen, which were coalescing to form orangish well to ill-defined plaques on the buttocks, lateral aspect of thighs, and elbows [Figure 1a and b]. There was no involvement of palms and soles, and nails were normal.

A skin biopsy was taken which revealed follicular plugging, alternating hyperkeratosis, and parakeratosis in a checkerboard pattern with a mild superficial perivascular and perifollicular lymphocytic infiltrate [Figure 2]. The patient was started on emollients and topical mometasone furoate 0.1% cream. There was significant improvement in her skin eruption and the patient could be continued on ponatinib therapy. The patient did not have recurrence of lesions on follow-up.

While most cases of PRP are sporadic and do not have any known etiology, few drugs have been implicated in triggering PRP-like rashes, such as TKIs, imiquimod, phosphoinositide 3-kinase inhibitors, ofatumumab, idelalisib, telaprevir, sofosbuvir, ramipril, pembrolizumab, bevacizumab, insulin, simvastatin, and infliximab.[3] TKIs, since their introduction, have significantly improved the morbidity and mortality in hematological malignancies. Ponatinib has proven to be indispensable in patients of CML who have not responded to earlier generations of TKIs, especially in patients harbouring T315I mutation.[2] Apart from tyrosine kinase, ponatinib also acts on fibroblast growth factor, Feline McDonough Sarcoma (FMS) like tyrosine kinase-3, receptor tyrosine kinase (KIT proto-oncogene), platelet-derived growth factor, vascular endothelial growth factor, and the steroid receptor coactivator (SRC) families.[1] While the newer

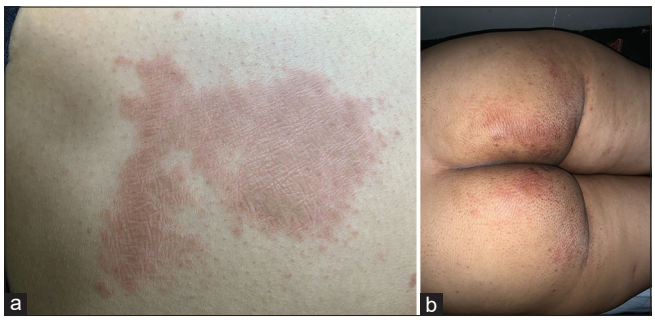

Figure 1: Folliculo-centric erythematous papules coalescing to form plaques with an orangish hue on the (a) lateral aspect of thigh and (b) buttocks

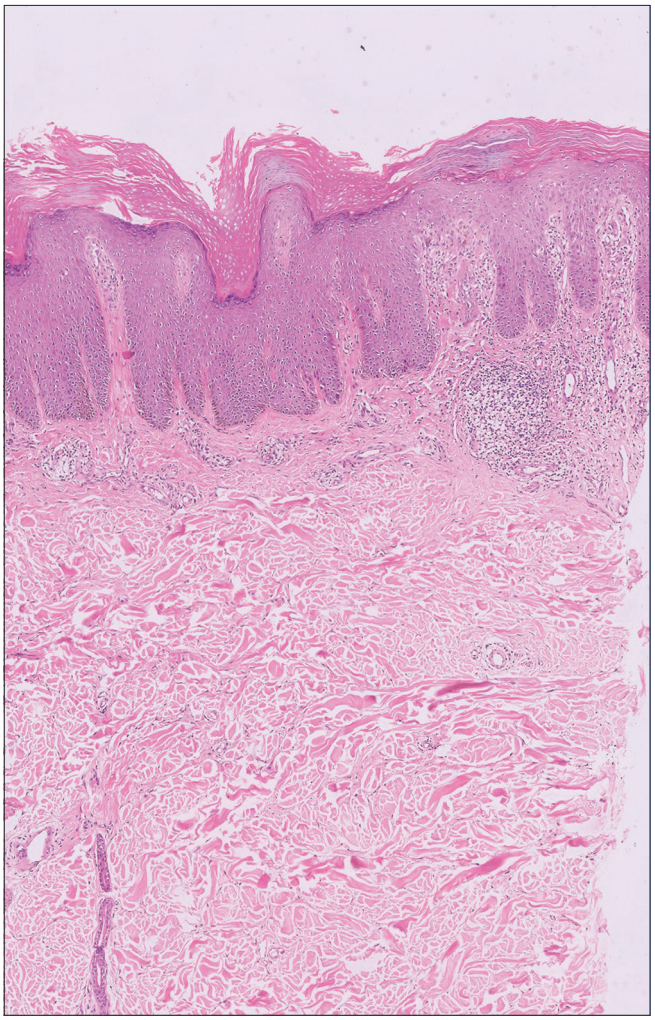

Figure 2: Follicular plugging, alternating hyperkeratosis and parakeratosis in a checkerboard pattern with a mild superficial perivascular and perifollicular lymphocytic infiltrate (H and E, 10X)

targeted therapies have much lesser systemic side effects, they are notorious for causing a plethora of cutaneous adverse effects including but not limited to rash, dryness, dyspigmentation, and icthyosis.[2,4]

Ten cases of ponatinib induced PRP-like rash have been reported to date [Table 1].[5-10] The onset of rash is between 1 week and 5 months after starting the drug. The diagnosis is usually clinical and supported by dermoscopy and

Table 1: Summary of literature review on ponatinib-induced pityriasis rubra pilaris

Study	Age and gender	Indication for ponatinib	Onset of rash	Morphology and distribution of rash	Treatment given	Response
Jack *et al*.[5]	53/M	CML unresponsive to imatinib, dasatinib, and nilotinib	2-3 months	Well-demarcated pink-yellow thin papules coalescent into plaques with scale and islands of sparing on the trunk, buttocks, arms, proximal legs and axillae	Acitretin 25 mg daily followed by acitretin 10 mg daily with narrowband UVB phototherapy, keratolytic	Near complete resolution
Alloo *et al*.[6]	59/M	Refractory metastatic GIST	2 weeks	Red–orange, follicular-based papules and plaques with bran-like, powdery white scale over his thighs and axillae	Topical triamcinolone 0.1% cream	Near complete resolution
Alloo *et al*.[6]	79/M	Treatment-refractory CML	4 weeks	Pink–orange, thin plaques on the proximal arms, axillae, and lateral breasts, and thin plaques with scale on the scalp	Hydrocortisone 2.5% cream, emollients, ketoconazole shampoo, topical tazarotene	Complete resolution with tazarotene
Alloo *et al*.[6]	65/M	Metastatic GIST	10 days	Pink, follicular-based papules on the trunk and proximal thighs, and follicular prominence with hyperkeratotic spicules over his beard area and eyebrows	Ketoconazole shampoo, clobetasol 0.05% solution for scalp, topical tretinoin 0.1% cream for face and trunk and emollients	Significant improvement
Alloo *et al*.[6]	72/M	Metastatic GIST	7 days	Perifollicular erythema with prominent follicular hyperkeratotic spicules over the chest and abdomen	Ammonium lactate 12% cream	Marked improvement
Alloo *et al*.[6]	62/F	Metastatic GIST	2 weeks	Orange-red, plate-like, annular plaques with islands of sparing on bilateral cheeks, submental and posterior neck, upper back and bilateral upper arms with scalp erythema and scale and plate-like, xerotic patches on the lateral thighs	Ketoconazole shampoo, topical steroids and emollients, topical tazarotene	Near complete resolution after addition of tazarotene
Eber *et al*.[7]	50/F	CML refractory to interferon, imatinib, dasatinib, and bosutinib	4 weeks	Xerotic, atrophic, and ichthyosiform pink plaques involving the bilateral axillae, proximal thighs and abdomen	Tretinoin 0.025% cream	Complete resolution
Krygier *et al*.[8]	60/F	Recurrent acute lymphoblastic leukemia	6 weeks	Erythematous-scaly plaques with orange-red tones, located on the back, abdomen, breasts, and upper limbs, with islands of sparing	Mometasone furoate 0.1% cream, emollient	Complete resolution
Kamat *et al*.[9]	52/F	BCR/ABL positive CML which failed to respond to the first-line treatment	3 weeks	Irregular ichthyosiform atrophic plaques over upper chest and neck with islands of sparing.	Topical tazarotene 0.05% cream, acitretin 25 mg, emollients	Near complete resolution
Mongereau *et al*.[10]	66/F	CML with failure of previous therapies with hydrea, dasatinib, nilotinib, bosutinib, and imatinib	3 weeks	Slightly scaly erythematous and salmon-colored plaques with sharp borders located in the axillary and submammary folds, abdomen, and on the shins.	High-potency topical steroid, urea-based keratolytic preparation	Significant improvement

UVB=Ultraviolet-B, CML=Chronic myeloid leukemia, GIST=Gastrointestinal stromal tumor

histopathological examination. The mechanism of TKIs causing PRP is not clearly understood. Dysregulation of downstream inflammatory pathways leading to alteration of cutaneous regulatory immune surveillance and aberrant epidermal growth has been postulated.[6]

Drug-induced PRP is usually localized and can be controlled with topical therapy if detected and managed early. The first-line agents used for drug-induced PRP are topical steroids, topical retinoids, keratolytics, and emollients. In case of widespread disease, oral retinoids and whole-body narrow band ultraviolet B have been successfully tried.

With the advent of more new drugs, it is important to have an in-depth knowledge of their various cutaneous adverse effects. The indolent nature of drug-induced PRP most often warrants only topical treatment, such as corticosteroids. Discontinuation of life-saving chemotherapeutic drugs can be avoided by timely and appropriate management of their adverse effects.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Pavlovsky C, Chan O, Talati C, Pinilla-Ibarz J. Ponatinib in the treatment of chronic myeloid leukemia and philadelphia chromosome positive acute lymphoblastic leukemia. Future Oncol 2019;15:257-69.
2. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre PD, Paquette R, Chuah C, *et al*. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: Final 5-year results of the phase 2 PACE trial. Blood 2018;132:393-404.
3. Mufti A, Lytvyn Y, Maliyar K, Sachdeva M, Yeung J. Drugs associated with development of pityriasis rubra pilaris: A systematic review. J Am Acad Dermatol 2021;84:1071-81.
4. Thakur V, Malhotra P, Lad D, Chatterjee D, Vinay K, Dogra S. Ponatinib-induced lamellar ichthyosis-like eruption. Int J Dermatol 2020;59:e156-7.
5. Jack A, Mauro MJ, Ehst BD. Pityriasis rubra pilaris-like eruption associated with the multikinase inhibitor ponatinib. J Am Acad Dermatol 2013;69:e249-50.
6. Alloo A, Sheu J, Butrynski JE, DeAngelo DJ, George S, Murphy GF, *et al.* Ponatinib-induced pityriasiform, folliculocentric and ichthyosiform cutaneous toxicities. Br J Dermatol 2015;173:574-7.
7. Eber AE, Rosen A, Oberlin KE, Giubellino A, Romanelli P. Ichthyosiform pityriasis rubra pilaris-like eruption secondary to ponatinib therapy: Case report and literature review. Drug Saf Case Rep 2017;4:19.
8. Krygier J, Leemans G, Forsyth R, de Becker A, Gutermuth J, Grosber M. A new case of pityriasis rubra pilaris-like eruption associated with ponatinib, a tyrosine kinase inhibitor. Ann Dermatol Venereol 2018;145:665-70.
9. Kamat D, Chatterjee D, Mahajan R. Ponatinib-induced atypical pityriasis rubra pilaris-like rash. Indian J Dermatol Venereol Leprol 2020;86:688-90.
10. Mongereau M, Hillion B, Fouillard L, Boivin JF, Gaudron S. Pityriasis rubra pilaris-like reaction induced by a tyrosine kinase inhibitor, the ponatinib. Am J Dermatopathol 2021;43:394-5.

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